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Plantwide Design and Economic Evaluation of Two Continuous Pharmaceutical Manufacturing (CPM) Cases: Ibuprofen and Artemisinin

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Abstract

Continuous Pharmaceutical Manufacturing (CPM) is a rapidly expanding research field with growing industrial importance: challenging the current batch production paradigm, it has a documented potential to deliver key cost, efficiency and environmental benefits. Ibuprofen, the potent painkiller, and artemisinin, a highly effective anti-malarial drug, have been identified as promising CPM candidates, and steady-state flowsheet models have been developed on the basis of published continuous organic synthesis pathways. Reactor design has been conducted using original kinetic parameter estimation results. A comparative economic analysis via published recoveries has computed performance indices which indicate that both CPM designs exhibit high economic potential, even if conservative profit and climate estimates are used to derive capital and operating costs. More detailed technoeconomic analyses can facilitate quicker CPM implementations.

Keywords: Continuous Pharmaceutical Manufacturing (CPM), ibuprofen, artemisinin.

1. Introduction

Continuous Pharmaceutical Manufacturing (CPM) is a vibrant research field addressing challenges due to the ever-increasing R&D costs and globalised corporate competition. Offering a cost-effective alternative to traditional batch processes (Roberge et al., 2008), CPM can reduce cost (Schaber et al., 2011) at high yield, solvent and energy efficiency, allow for easier process scale-up and eliminate intermediate storage needs, while also reducing environmental impact and increasing sustainability (Poechlauer et al., 2013). Process synthesis, modelling and simulation can rapidly assess process potential (Gerogiorgis & Barton, 2009) toward sound CPM business cases (Gernaey et al., 2012). Recently, a series of Active Pharmaceutical Ingredients (APIs) have been identified as promising CPM candidates (Jolliffe & Gerogiorgis, 2015): ibuprofen and artemisinin ranked highest among all, using a set of nine specific technoeconomic criteria (Figure 1)

Ibuprofen is recognised as an essential non-steroidal anti-inflammatory drug (NSAID) by the World Health Organisation; its global annual production exceeds 13,500 tonnes. Artemisinin is the parent substance of the fastest acting and most effective anti-malarial drugs, currently extracted in batch from sweet wormwood, *Artemisia annua* (Tu, 2011). Demand fluctuations and production timescales induce supply and cost unpredictability: between 2005 and 2008, market price varied by an order of magnitude, \$120–1,200/kg (Artemisinin Enterprise, 2008), with a recent report at \$400/kg in 2013 (Peplow, 2013). This paper focuses on a technoeconomic CPM analysis and comparison of these APIs. Process mass balance simulations for two CPM designs have been performed, and reactor design has relied on novel kinetic and thermodynamic parameter estimations. Annual capacity for both APIs (50 kg) is chosen toward comparative economic analysis.

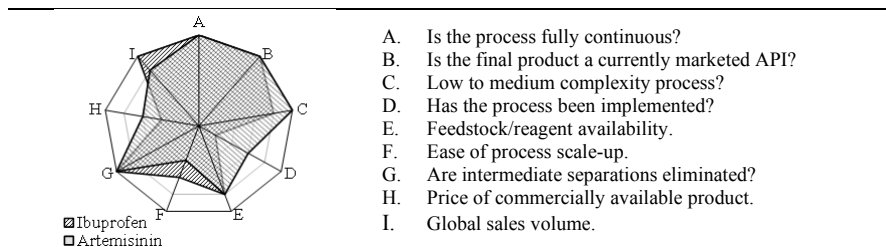


Figure 1. Systematic analysis of CPM potential for the two APIs (Jolliffe & Gerogiorgis, 2015).

2. Continuous flow synthesis of APIs

Continuous organic flow synthesis pathways for ibuprofen (Bogdan et al, 2009) and artemisinin (Kopetzki et al, 2013) illustrate their acknowledged therapeutic importance and serve as precedents for developing both steady-state process models reported here.

2.1. Ibuprofen

Ibuprofen is produced using three reactors: in the first PFR, Friedel-Crafts acylation converts isobutyl benzene (IBB) into intermediate **2_A**, then transformed in the second PFR (by 1,2-aryl migration) into intermediate **3_A**. The latter undergoes base hydrolysis in the third PFR, yielding the potassium salt of ibuprofen: we consider this entirely acidified prior to final separation, as the salt is unsuitable for commercial formulations.

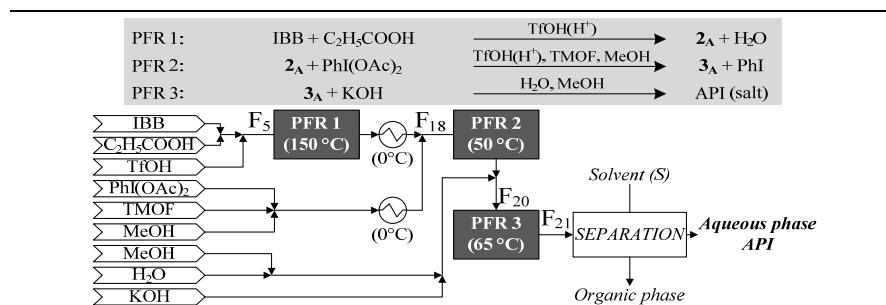


Figure 2. Demonstrated process flowsheet for ibuprofen CPM production (Bogdan et al, 2009).

2.2. Artemisinin

Artemisinin is attainable via a series of two reactors: dihydroartemisinic acid (DHAA, a conventional artemisinin batch extraction waste) is photo-oxidised in a chilled PFR, producing intermediate **3_B** and by-products. In the second PFR, **3_B** undergoes multiple transformations in presence of trifluoroacetic acid (TFA, acid catalyst), before eventual oxidation to artemisinin; additional by-products are generated (Gilmore et al., 2013).

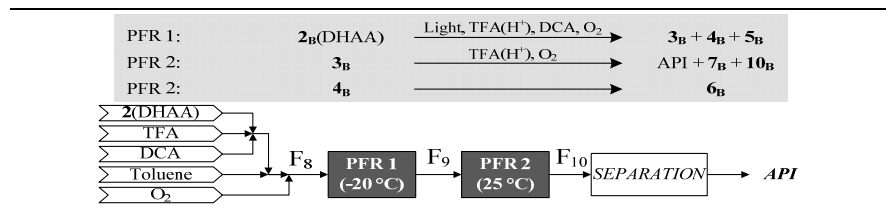


Figure 3. Demonstrated process flowsheet for artemisinin CPM production (Kopetzki et al, 2013).

3. Mass balances and reactor design

Process mass balances for both CPM flowsheets appear in Fig. 4; some flows are scaled for clarity, and by-products (BPD: salts, methyl formate, iodobenzene) are all grouped. For comparative economic evaluation, the annual production is set at 50 kg of pure API without considering any losses in downstream processing or final dosage formation. The summary of essential kinetic parameters for PFR design is presented in Table 1.

3.1. Kinetics

Kinetic rate constants and conversions for the first two ibuprofen reactions are extracted from literature data, using SPARC software for the third (Jolliffe & Gerogiorgis, 2015). Possible side effects (e.g. esterification reactions between organic acids and methanol), the chemical action of by-products and the presence of solids are assumed negligible; reaction orders and constants (hr^{-1} / 1st order, $\text{Lmol}^{-1}\text{hr}^{-1}$ / 2nd order) are given in Table 1.

Kinetic parameter estimation for both artemisinin reactions has relied on the first-order assumption, given their nature (large organic molecules react with an excess of e.g. O_2); published conversion and reactor volume data have been used (Kopetzki et al., 2013). The photo-oxidation reaction in the first PFR can achieve a DHAA conversion of 98%. For the second PFR, a conversion of 79% is obtained for the first reaction ($3_B \rightarrow \text{API}$), using DHAA conversion (98%), artemisinin (59.9%), 7_B (4.5%) and 10_B (2.5%) yields.

The conversion of 4_B (61%) is similarly calculated on the basis of data for overall yield (i.e. including species from the reaction of 3_B) of 6_B (6.18%) (Kopetzki et al., 2013); yields have been adjusted to account for small by-product (BPD) quantities ($< 1\%$ mol).

3.2. Reactor design

For both CPM plant designs, the present design analysis considers that all PFR reactors perform well at isothermal operation and that sufficient heat transfer can be achieved. Selecting a suitably small diameter ensures radial temperature gradients are negligible. Well-circulating heating media and controlled environments (e.g. ovens, baths) are established state of the art for several CPM reactor prototypes (Bedore et al., 2010).

Plug Flow Reactor (PFR) design has been performed by determining required lengths via integration: a small ID (5 mm) has been selected to ensure adequate heat transfer, in accordance with proven CPM PFR designs at similar length scale (Mascia et al., 2013). No phase change during flow is considered (precipitation can be prevented by design).

Table 1. Continuous reaction parameter estimates and summary of reactor (PFR) design results.

PFR # (reaction)	T (°C)	k_i (resp. units)	Flowrate (g hr^{-1})	Conversion (%)	ID (mm)	Volume (mL)	Length (mm)
<i>Ibuprofen</i>							
PFR 1 ($\text{IBB} \rightarrow 2_A$)	150	31.41	41.58	91	5.0	6.392	326
PFR 2 ($2_A \rightarrow 3_A$)	50	2732.3	115.77	98	5.0	1.997	102
PFR 3 ($3_A \rightarrow \text{API}$)	65	15.57	306.90	99	5.0	28.912	1472
<i>Artemisinin</i>							
PFR 1 ($\text{DHAA} \rightarrow 3_B$)	-20	39.12	109.86	98	5.0	10.442	532
PFR 2 ($3_B \rightarrow \text{API}$)	25	2.91	109.86	79	5.0	55.685	2836
($4_B \rightarrow 6_B$)	25	1.78	109.86	61	5.0	55.685	2836

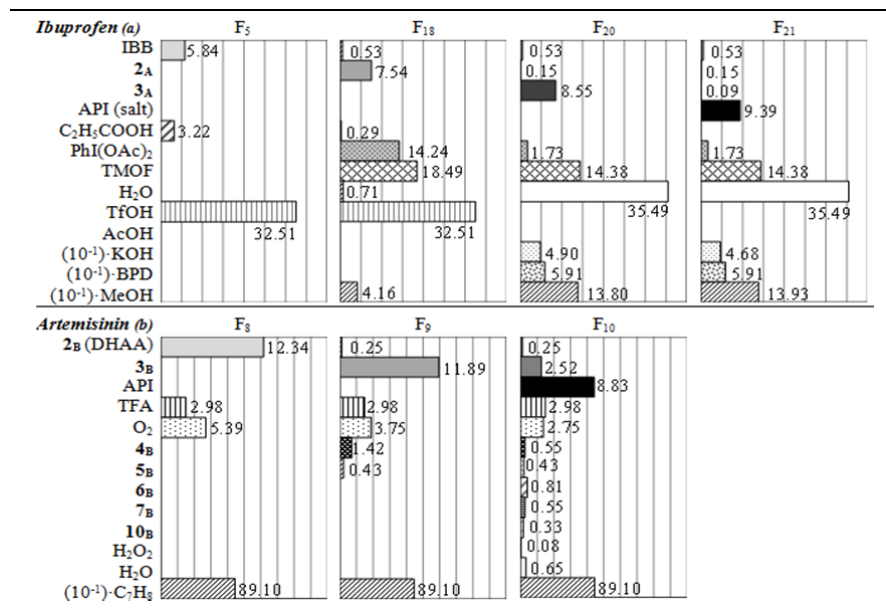


Figure 4. Mass balances for streams of both CPM designs (units: 5 g hr⁻¹/a, 2 g hr⁻¹/b).

4. Separation design

Separation design entails the analysis of candidate solvents and operating conditions: for ibuprofen production, liquid-liquid extraction (LLE) has been considered as a viable choice, to achieve high API recovery before crystallisation and downstream processing. Six solvents (acetonitrile, ethanol, methyl acetate, ethyl acetate, n-hexane, toluene) have been evaluated to assess performance and environmental impact (Alfonsi et al, 2008). Solvent-to-feed mass ratios (S:F₂₁) ranging from 0.25 to 5 have been considered for the ones yielding phase split (n-hexane, toluene), at 25 °C (ambient) and 65 °C (PFR3). Stream F₂₁ is approximated as a H₂O-MeOH mixture; solubility and phase equilibria modelling enables computation of effluent compositions (Jolliffe & Gerogiorgis, 2015).

The recommended choice is toluene, at a S:F₂₁ ratio of 0.75 at 25 °C, resulting in 81.7% final ibuprofen recovery: operation at higher temperature (65 °C) gives higher recovery, but is less preferable due to heating cost and off-gassing (Jolliffe & Gerogiorgis, 2015). While n-hexane performs better in many instances of S:F₂₁ ratios and temperatures, it has a grave environmental impact and is not a desirable solvent (Alfonsi et al, 2008). The other solvents considered are unsuitable for this LLE case due to full miscibility. Purification design must consider seamless downstream (e.g. ethanol-based) processing.

Kopetzki et al. (2013) used acetonitrile to dissolve artemisinin, allowing the removal of poorly-soluble DCA by filtration: the latter is followed by two crystallisation stages, both of which use a cyclohexane-ethanol (9:1 v/v) solvent mixture to obtain solid API. The published organic flow synthesis pathway produces artemisinin at a yield of 65%; the subsequent sequential crystallisations achieve respective yields of 57% and 46%, corresponding to an overall API recovery of 70.8%: this can also be improved further to increase CPM efficiency, by means of multicomponent equilibria and solubility models.

5. Environmental impact: the E-factor

The environmental factor (E-factor) is a green engineering metric of process impact: in its simplest form, it is defined as the ratio of waste to product mass (Sheldon, 2012). Highly efficient continuous (e.g. petrochemical) industries have typical E-factors of 0.1, while pharmaceutical industries frequently reach values of 200 or higher (Ritter, 2013). E-factors have been calculated for both CPM designs considered: a very attractively low low E-factor of 25.4 has been calculated for ibuprofen (Jolliffe & Gerogiorgis, 2015), indicating that CPM implementation is a viable option even without solvent integration. The corresponding E-factor of 33.5 for artemisinin is equally appealing (albeit slightly higher): the total mass of material input considers both feedstocks as well as solvent (cyclohexane-ethanol) requirements for both crystallisation stages and API production. The comparable and similar E-factor values underline the importance of systematic environmental impact evaluation, while also illustrating that there is indeed clear scope for improving the efficiency of artemisinin recovery by continuous separation design.

6. Economic evaluation

Economic CPM performance has been analysed using established economic metrics, Net Present Value (NPV), Return on Investment (ROI), and Payback period (PBP); for these, the plant lifetime, τ (20 yr), and the discount rate, r (variable) are key parameters. Prices are taken as £538/kg and £229/kg for ibuprofen and artemisinin, respectively. For CapEx calculations, all equipment costs have been sourced from vendor databases. For ibuprofen, unit prices of all expensive equipment as listed by Bogdan et al. (2009) have been considered and scaled up accordingly; for artemisinin production, a literature figure for equipment cost of similar capacity has been used (Extance, 2012). Assumptions include: equipment delivery cost 5% of price, working capital 3.5% of annual sales, contingency 20% of the battery-limits installed cost (BLIC, i.e. equipment plus delivery) (Schaber et al., 2011); total CapEx is the sum of BLIC and contingency. For OpEx calculations, waste disposal costs £0.33 and £1.98 per litre of water and of solvent have been considered, respectively; utility cost is £0.96 per kg of input material (Schaber et al., 2011). Labour, material handling, tax and quality control have not been considered, but are essential components of a more detailed technoeconomic analysis. Annual operation is set at 7728 and 8000 hr for ibuprofen and artemisinin, respectively. Economic performance indices for CPM design evaluation are summarised in Table .

Table 2. Economic performance comparison for CPM production of both APIs analysed ($r=5\%$).

	Ibuprofen	Artemisinin
NPV	£73,500	£108,300
ROI (%)	33.95	82.60
PBP (years)	3.27	1.28
BEP (kg API/year)	7.37	3.03

Artemisinin has a stronger economic potential (higher NPV and ROI), reaching payback (positive NPV) in less than half the time (Fig. 5). Nevertheless, both CPM designs are clearly viable, even if Table values are only useful in preliminary economic evaluation (implementation requires a comprehensive analysis of all equipment and cost factors). The CPM of artemisinin is very attractive as it uses as feedstock waste material from the current artemisinin extraction process: great added value is attainable by implementing this CPM design to address demand. The CPM of ibuprofen is also promising, but a strong competitive advantage is essential to demonstrate in case of no patent protection.

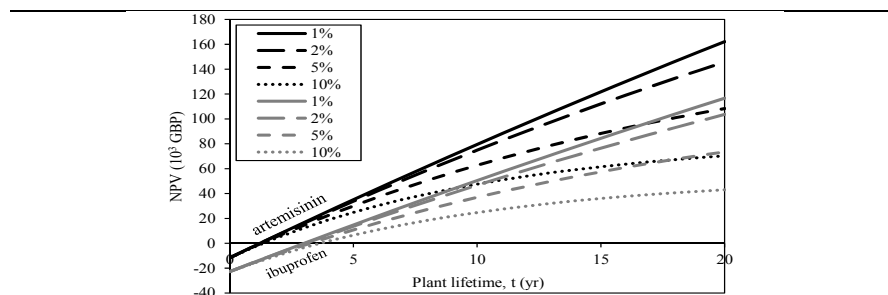


Figure 5. Comparison of projected Net Present Values (NPV) for a wide range of discount rates.

7. Conclusions

Continuous Pharmaceutical Manufacturing (CPM) has great potential to deliver strong cost and efficiency benefits for two APIs (ibuprofen and artemisinin) at a 50 kg/yr scale. Computed PFR volumes range from 2–55 mL, illustrating CPM applicability benefits, with a positive environmental impact outlook (E-factors of 25.4 and 33.5, respectively), and the enormous sustainability benefit of using batch process waste as CPM feedstock. Both designs thus hold high economic promise (NPV: £73,500 and £108,300, ROI: 34% and 83%, PBP: 3.3 yr and 1.3 yr, respectively) toward CPM pilot plant implementation.

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